TITLE PAGE FOR ON-LINE DATA SUPPLEMENT

Title: Efficacy of Positive Airways Pressure and Oral Appliance in Mild to Moderate Obstructive Sleep Apnea

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METHODS

Study Design

A randomized, placebo-controlled three-way crossover trial was conducted in two Australian centres (Austin Health, Melbourne, Victoria and Repatriation General Hospital Daw Park, Adelaide, South Australia) to investigate daytime sleepiness, neurobehavioral function and blood pressure in patients with mild to moderate obstructive sleep apnea (OSA) and to assess the response to 3 months treatment with each of nasal continuous positive airways pressure (nCPAP), mandibular advancement splint (MAS) and a placebo tablet The Human Research Ethics Committees of the two centres approved the project and written informed consent was obtained from each subject.

OSA subject eligibility was similar to our previously reported study of CPAP in mild OSA patients(E1), with the addition of criteria for MAS usage. All subjects had been referred for investigation of symptomatic sleep-disordered breathing They were examined by a dentist at the beginning of the trial (NV and CM), and were excluded if they did not have at least 2 teeth in their upper and lower jaws on both left and right sides to enable adequate retention of the MAS. If dental caries were found, subjects were advised that these would require treatment prior to MAS usage.

Subjects received in randomised order CPAP (Sullivan Elite, ResMed Limited, Sydney, Australia), a mandibular advancement splint (Medical Dental Sleep Appliance, RJ & VK Bird, Melbourne, Australia) and a placebo lactose tablet. Each treatment was given for 3 months. Randomisation was conducted by blindly selecting one of six pieces of paper from a

box. On each piece of paper were written instructions to follow one of the six possible treatment orders. The paper was then replaced in the box in preparation for the next patient randomisation. There was a 2 week intervening washout period between each treatment to prevent any carryover effects. Subjects were told that the tablet was intended to improve airway function during sleep and were instructed to take it immediately prior to going to bed. We chose to use an oral placebo because we required a placebo for both CPAP and MAS, and neither sham CPAP or sham MAS would have been equally valid for both active treatments. At the beginning of the trial and at the end of each 3-month treatment period, subjects underwent overnight polysomnography, a Maintenance of Wakefulness Test, 24-hour ambulatory blood pressure measurement, echocardiography, neurobehavioral assessment and completed the Epworth Sleepiness Scale, quality of life, subjective sleepiness and symptom questionnaires (Table One, Appendices One and Two). Additionally, the first 18 OSA subjects to complete the trial had overnight polysomnography performed at the end of each washout period, prior to commencing the next treatment to ensure that a 2-week washout period was adequate for sleep study variables to return to baseline (Fig 2).

Standardization and Calibration of Measurements between the two Centers

Prior to commencement of the project, protocols for overnight polysomnography, the administration of Maintenance of Wakefulness Tests and the administration of the neurobehavioral tests were standardized between the two centers. One trained researcher at each institution administered the neurobehavioral tests in a blinded manner; two scorers at one center and one scorer at the other center performed sleep study scoring. To measure intra- and inter-scorer reliability, each scorer scored the same 10 studies twice. Interscorer reliability of the apnea-hypopnea and arousal indices were calculated using the intraclass

correlation coefficient; estimation of the intrascorer reliability was calculated using paired T-tests. The intraclass coefficient (using Cronbach (alpha) and one-way random effect models) was 0.94 (95% CI 0.86, 0.98) for the AHI and 0.66 (95% CI 0.42, 0.88) for arousal index. Intrascorer paired T-test p values for AHI and arousal index were 0.31 and 0.89 respectively for scorer 1 (SB), 0.52 and 0.24 for scorer 2 (SR), and 0.64 and 0.26 for scorer 3 (MS). A percent positive agreement score for epoch-by-epoch sleep study staging was calculated, and was between 82% and 94% (mean 87.3%, SEM 1.4%).

Polysomnography

Overnight polysomnography was performed as previously described(E1). The MWT was performed according to the standard guidelines(E2) on the day following polysomnography.

Implementation of CPAP

CPAP was implemented during an overnight sleep study. Subjects were fitted with a comfortable mask and familiarized with the CPAP pump. After sleep onset, CPAP was commenced at 4cmH_2O pressure and increased in increments of 1cmH_2O until all respiratory events were abolished. In the morning, subjects were supplied with a pump and mask to commence treatment that evening.

Fitting of Mandibular Advancement Splint

OSA subjects received a fully-adjustable custom-made Medical Dental Sleep Appliance (RJ & VK Bird P/L, Melbourne, Australia) This device is made from 3mm dual laminate (Hard/Soft) functional splinting material, with a hook attached to the upper shelf and a ledge attached to the lower shelf. The hook and ledge interconnect and and the lower plate is

advanced by means of a screw, with a maximum of 12mm protrusion in 0.25mm increments (48 possible adjustments). Subjects were assessed by a dentist at each site (CM and NV) prior to inclusion in the trial for adequacy of dentition and oral hygiene. One subject with dental caries had not had his caries treated and so was excluded from the trial when he reached the MAS arm. Using a George gauge, the dentist measured the resting occlusal position and maximal possible voluntary jaw protrusion. The goal of MAS advancement was maximal comfortable protrusion. At the initial fitting, the MAS was advanced maximally as tolerated by the subject. Subjects were reviewed weekly by the dentist and the MAS advanced further, to the limit of patient comfort. When no further advancement was possible, the screw was sealed, the position of advancement measured, and the 3 month treatment period commenced. No further adjustments were made to the MAS. The wash-in period for the MAS ranged from 1-3 weeks. During the treatment time, subjects were telephoned regularly and asked about side-effects (graded as none, mild, moderate or severe) and subjective efficacy (improved, unchanged, worse). These data will be presented in a later report.

Analysis of Sleep Data

All polysomnograms and Maintenance of Wakefulness Tests were manually staged using standard criteria(E3, E4) with 30-second epochs.

The MWT consisted of four forty-minute nap opportunites under standard conditions at least 2 hours apart throughout the day, and with the first test at least 2 hours after wakening from sleep. It was scored with sleep being defined as 3 epochs of stage 1 or 1 epoch of any other sleep stage. Subjects were woken immediately they fell asleep, and the test terminated(E2). Prior to each MWT nap opportunity, subjects completed the Stanford Sleepiness Scale(E5)

and a visual analogue scale to assess subjective alertness and well-being (Appendix One, On-Line Supplement).

Outcome Assessment

Neurobehavioral Function

The neuropsychological tests used consisted of a selection from the Neuropsychological Assessment Battery(E7) (NAB) and paper-based tests as shown in Table 1 and as used in our previously published study(E1). The complete session required approximately 1 hour of patient time. To minimize any learning effect due to test repetition, subjects attended a familiarization session 1 week prior to the baseline assessment, and performed an abbreviated version of these tests. Quality of life was assessed with two questionnaires we have used and described previously(E1) and completed by subjects on the day of their MWT.

Cardiovascular Assessment

Systemic blood pressure over 24 hours was measured as described in our previous study(E1). Echocardiography was performed using the Acuson XP system (Acuson Corporation, Mountain View, California) and a 2.5mHz transducer to measure pulmonary artery pressure and left ventricular mass. The pulmonary artery pressure was calculated from the regurgitant tricuspid jet, if present, and the left ventricular mass was calculated from a standardized measurement of the left ventricular wall thickness. For the purposes of this analysis, hypertensive subjects were defined as having mean 24 hour systolic blood pressure ≥140mmHg and/or mean 24 hour diastolic blood pressure ≥ 90mmHg. The blood pressure "dipping ratio' was defined as nighttime mean arterial pressure/daytime mean arterial pressure(E10). "Non-dippers" were subjects whose mean arterial blood pressure did not fall

by at least 10% during the night, ie dipping ratio ≥0.90. Thus a higher dipping ratio indicates physiological impairment.

Other Measurements

Age, gender, medications, height, weight, neck, waist and hip circumferences, level of education and pulmonary function tests were recorded.

Treatment Adherence

Usage of all treatments was measured. ResMed Sullivan Elite CPAP pumps were used, with inbuilt compliance monitoring as previously described(E1). Subjects were asked to keep a diary of their MAS usage, in which they recorded nightly use as well as any problems or side effects they were experiencing. In the placebo arm, subjects were issued with a bottle containing 100 capsules for the 3 month treatment period. Adherence was estimated by counting the remaining capsules when subjects returned the bottle at the end of this treatment period. To maximize treatment adherence, each subject in each treatment arm was telephoned 3 days after starting treatment, reviewed in person after 1 week and telephoned monthly thereafter to discuss and resolve problems and to encourage nightly use of the treatments.

Treatment Preference

At the conclusion of the study, each subject and their domestic partner was asked to answer three questions which assessed treatment preference. We asked "With which treatment could you live most easily?", "Which treatment do you think worked best to treat your (your partner's) sleep apnea symptoms?" and "Which treatment would you prefer to (be) use(d) to

treat your (your partner's) sleep apnea?". Subjects and domestic partners ranked each of the three treatments for each of these questions.

Statistics

The Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, version 11.0, 2001) database program was used. Power and sample size calculations were performed(E11) using ESS as the primary outcome variable, and a minimum clinically meaningful change in the Epworth Sleepiness Scale of 2 between treatments. For a paired comparison, study power of 90% and α=1%, sixty-two subjects were required. Post-hoc power calculations confirmed that our sample size was adequate to detect a change as small as ½ standard deviation in the ESS and most of our neurobehavioral outcomes.

An intention to treat analysis of treatment response was used. All data collected were included. With 114 OSA subjects the maximum possible number of data points was 456 (114x4), but due to dropouts there were only 374 data points (82.0%). Missing value analysis showed that the missing data were random, therefore missing values were imputed using an iterative maximum likelihood estimation technique applied to valid values of other variables and cases(E12).

Treatment responses were compared using repeated measures ANOVA with Bonferroni correction, thus a p value of 0.08 was required to reach statistical significance. Due to the large number of response variables, a two-stage factor analysis was also performed. In the first stage, the outcome variables were placed into one of the following categories: Cardiovascular measures, Sleepiness, Vigilance, Memory, Mood, other Neurocognitive function, Symptoms, Quality of Life and Disease Severity. Factor analysis was run within

each category, and we selected the 1, 2 or 3 variables that appeared to best summarise the data in that category (ie by discarding variables with very low uniqueness, keeping those with high loadings on particular factors). It was decided to omit pulmonary artery pressure data from analysis; 275 case observations were available with complete measurements of the other cardiovascular parameters, but the inclusion of pulmonary artery pressure reduced this to only 108.

The variables selected in the first stage were all then entered into a second stage factor analysis. At this stage left ventricular mass was excluded due to high uniqueness (>91%), suggesting a large proportion of measurement noise. Five significant factors were found and, after varimax rotation, scores for these factors were calculated for all subjects and measurement times using the Bartlett estimator, then normalized.

The magnitude of the treatment response from baseline for each of the five factors was also measured using effect sizes. This identifies clinically significant changes; however in that larger effect sizes mean larger differences, they will tend to correspond to smaller p values in a test of equality of means. An effect size of 0.20 is considered small, 0.50 is considered moderate and 0.80 is considered large(E13). To obtain an overview of which treatment each individual subject responded to best, we summed the 5 effect sizes.

A planned posthoc analysis of the subgroup of subjects with AHI 5-15 was performed to determine if the treatment response extended to this group of subjects with mild disease.

Appendix One **SLEEP APNEA SYMPTOM QUESTIONNAIRE**

NEVER ——————————X—————————— ALWAYS

1. How often do you snore?
2. Do you wake in the night with a choking feeling?
3. How often would you sleep more than 8 hours in total in a 24 hour period?
4. How often do you wake more than once during the night?
5. Do you have a headache when you wake up in the morning?
6. Have you noticed a reduction in your libido or sex drive?
7. Do you feel sleepy during the day?
8. Has anyone noticed that you momentarily stop breathing during sleep?
9. Do you fall asleep while reading?
10. Do you wake up in the morning feeling confused?
11. How often do you have a nap during the day?
12. Do you feel sleepy in the evenings?
13. Have you or anyone else noticed a change in your personality recently?
14. How often do you doze off or fall asleep while driving?

Appendix Two **SUBJECTIVE SLEEPINESS ASSESSMENT**

Stanford Sleepiness Scale

Tick the box next to the statement that best describes your level of alertness or sleepiness right now.

☐ Feeling active, vital, alert, wide awake.

☐ Functioning at a high level but not at peak, able to concentrate.

☐ Relaxed, awake but not fully alert, responsive.

☐ A little foggy, let down.

☐ Foggy, beginnin to lose track, difficulty in staying awake.

☐ Sleepy, prefer to lie down, woozy.

☐ Almost in reverie, cannot stay awake, sleep onset appears imminent

Visual Analog Scale

Place a cross (X) on the line to indicate how you are feeling right now.

1. How alert do you feel?

Very sleepy ——————————————— Very alert

2. How good do you feel?

Very bad ——————————————— Very good

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LEGEND FOR ON-LINE DATA SUPPLEMENT FIGURES

Figure E1 Mean systolic and diastolic blood pressure were calculated hourly for the baseline assessment and for each of the three treatment conditions. There was no significant difference between any of the four conditions at any time.

Figure E2 Subjects' and Partners' Treatment Preferences. Subjects found the placebo tablet easiest to use, but found that CPAP worked better and it was their preferred treatment, followed by MAS. Domestic partners had similar results, although fewer thought that placebo was the easiest treatment to live with and more thought that CPAP was the easiest to live with. Their overall preference was also for CPAP, closely followed by MAS.

TABLE E1 NEUROBEHAVIORAL TESTS

Pre-morbid Performance IQ	National Adult Reading Test - Revised (NART-R)
Memory	Word Pair Memory Recall*
	Logical Memory 1 & 2, immediate
	Digit Span forwards & backwards
Set Shifting	Trails A and B
	Digit Symbol Substitution Test *
	Controlled Oral Word Association Test.
Vigilance and Divided Attention	Psychomotor Vigilance Task*
	Stroop Color Association Test
	Paced Auditory Serial Addition Task
Mood Symptoms	Profile of Moods States*
	Beck Depression Inventory
Sleepiness	Sleep Apnea Symptom Questionnaire†
	Epworth Sleepiness Scale
	Maintenance of Wakefulness Test
	Stanford Sleepiness Scale
	Visual Analogue Scale - Sleepiness‡
Quality of life	SF-36 questionnaire
	Functional Outcomes of Sleep Questionnaire

* Neuropsychological Assessment Battery

† Developed in-house, see Online Supplement, Appendix One

‡ Developed in-house, see Online Supplement, Appendix Two

TABLE E2 POLYSOMNOGRAPHY OUTCOMES.

	Baseline Mean (SEM)	CPAP Mean (SEM)	MAS Mean (SEM)	Placebo Mean (SEM)
Apnea Hypopnea Index	21.3(1.3)	4.8(0.5) ‡,¶,** [6.1(0.6) impl]	14.0(1.1) ‡,¶	20.3(1.1)
Arousal Index	22.0(1.2)	18.3(0.9) †,¶,** [17.5(0.8) impl]	23.8(1.2)	25.2(1.1)
4% oxygen desaturation	12.4(1.5)	1.6(0.2) ‡,¶,**	8.1(1.3) ‡,¶	12.5(1.6)
Minimum Oxygen Saturation, %	86.7(0.6)	91.9(0.3) ‡,¶,**	87.8(0.4) ¶	85.4(0.6)
Desaturation < 90%, % TST	2.4(0.5)	0.2(0.1) ‡,¶,**	1.6(0.4)	2.0(0.4)
TST, minutes	321.1(6.2)	329.7(5.0)	335.1(4.7)*	335.9(4.7)*
Stage 1 (% TST)	12.8(0.9)	9.2(0.5) †,π	10.8(0.8) †,§	12.3(0.8)
Stage 2 (%TST)	50.5(1.0)	51.1(0.9)	49.2(0.9)	50.2(1.0)
Stage 3 & 4 (%TST)	17.9(1.2)	20.7(1.1) ‡,§	20.1(1.1)*	18.5(1.2)
REM sleep (%TST)	18.8(0.7)	18.9(0.5)	19.8(0.6)	18.9(0.6)
Sleep Efficiency (%)	79.5(1.1)	82.1(0.8)*	82.0(1.0) †	80.7(0.9)

Definition of Abbreviations: impl = CPAP implement polysomnogram; 4% oxygen desaturation = number of oxygen desaturations of at least 4%, per hour of sleep; Desaturation <90% = percent of total sleep time when oxygen saturation is <90%; TST = Total Sleep Time.

	p<0.05	p<0.01	p<0.001
Compared to baseline	*	†	‡
Compared to placebo	§	π	¶
CPAP vs. MAS	**		

TABLE E3 DAYTIME SLEEPINESS AND SYMPTOMS

	Baseline	CPAP	MAS	Placebo
Epworth Sleepiness Scale	10.7(0.4)	9.2(0.4)‡,¶	9.2(0.4)‡,¶	10.2(0.4)
Maintenance of Wakefulness Test (mins)	30.7(0.9)	30.0(0.9)	29.6(0.9)	28.0(0.9)†
Stanford Sleepiness Scale	3.1(0.1)	2.7(0.1)‡,π	2.8(0.1)†,§	3.0 (0.1)
Sleep Apnea Symptom Questionnaire	64.7(1.7)	52.9(1.7)‡,¶	54.9(1.6)‡,π	60.1(1.5)†
Visual Analog Scale – Alertness	5.4(0.2)	6.1(0.1) ‡,¶	5.8(0.1)	5.5(0.1)
Visual Analog Scale – Well being	6.8(0.1)	7.1(0.1)	6.9(0.1)	6.8(0.1)

All data are mean(SEM)

	p<0.05	p<0.01	p<0.001
Compared to baseline	*	†	‡
Compared to placebo	§	π	¶
CPAP vs. MAS	**		

TABLE E4 NEUROPSYCHOLOGICAL FUNCTION AND MOOD

	Baseline	CPAP	MAS	Placebo
Word Pair Memory Recall	1.7(0.1)	2.0(0.1) ‡	2.0(0.1) ‡	2.0(0.1) ‡
Logical Memory Test	11.8(0.3)	13.2(0.3) ‡	13.2(0.3) ‡	13.5(0.3) ‡
Digit Span Backwards	4.4(0.1)	4.6(0.1)	4.6(0.1)	4.8(0.1)*
Trailmaking B	85.9(4.4)	73.3(3.3) ‡	76.0(3.7) *	74.2(3.6) ‡
Digit Symbol Substitution Task	46.4(0.4)	47.3(0.4)*	47.5(0.4) †	46.8(0.4)
COWAT	43.2(1.1)	46.5(1.2) ‡	46.3(1.1) ‡	46.3(1.0) ‡
PVT – 1/RT slowest 10%	2.7(0.1)	2.7(0.1) §	2.7(0.1)	2.6(0.1)
PVT errors	7.4(0.8)	7.4(0.7)	7.5(0.8)	7.8(0.8)
PVT lapses	2.5(0.3)	2.1(0.2) §	2.2(0.2)	2.7(0.3)
Stroop Color Association Test	4.8(0.8)	9.3(0.9) ‡	10.3(0.9) ‡	9.2(0.9) ‡
PASAT – 1.2	3.4(0.2)	2.9(0.1) *,π,**	2.6(0.03) ‡,¶	3.4(0.1)
PASAT – 2.4	4.2(0.2)	3.8(0.2) ‡	3.7(0.1) ‡	3.7(0.1) ‡
POMS – Total Mood Disorder	15.5(2.0)	6.3(1.7) ‡, π	9.7(2.1) *	11.8(2.1)
POMS – Tension Anxiety	5.7(0.4)	3.9(0.3) ‡,§	4.2(0.3) ‡,§	4.7(0.4) *
POMS – Depression Dejection	3.6(0.5)	2.1(0.3) †,§	2.9(0.5)	3.2(0.5)
POMS – Anger Hostility	2.3(0.3)	1.9(0.2)	2.3(0.4)	2.2(0.3)
POMS – Vigor Activity	12.1(0.8)	14.1(0.6) *, π	13.2(0.6)	12.8(0.6)
POMS – Fatigue Inertia	8.8(0.5)	6.8(0.5) ‡,§	7.5(0.5)	8.1(0.5)
POMS – Confusion Bewilderment	7.5(0.3)	5.9(0.3) ‡	6.0(0.3) ‡	6.4(0.3) ‡
Beck Depression Inventory	9.2(0.5)	6.7(0.5) ‡	6.9(0.5) ‡	7.7(0.6) †

All data are mean(SEM)

Definition of Abbreviations: COWAT = Controlled Oral Word Association Task; PVT = Psychomotor Vigilance Task; 1/Rtslowest 10% = inverse of the mean of the slowest 10% response times; PVT errors = the number of responses of less than 100mseconds; PVT lapses = the number of responses > 500mseconds; PASAT – 1.2 = Paced Auditory Serial Addition Task at the 1.2 second speed, time per response, seconds; POMS = Profile of Moods States

	p<0.05	p<0.01	p<0.001
Compared to baseline	*	†	‡
Compared to placebo	§	π	¶
CPAP vs. MAS	**		

TABLE E5 QUALITY OF LIFE OUTCOMES

		Baseline	CPAP	MAS	Placebo
FOSQ	Mean Score	3.1(0.1)	3.3(0.1) ‡,§	3.3(0.1) ‡,§	3.3(0.1) †
	General Productivity	3.2(0.1)	3.4(0.1) ‡	3.4(0.1) ‡	3.4(0.1) †
	Activity Level	3.0(0.1)	3.3(0.1) ‡,§	3.2(0.1)‡	3.1(0.1)*
	Sexual Relationships	2.9(0.1)	3.0(0.1)	3.0(0.1)	3.0(0.1)
	Social Outcome	3.3(0.1)	3.6(0.1) †	3.7(0.1)‡,¶	3.4(0.1)
	Vigilance Level	3.0(0.1)	3.2(0.1) ‡	3.1(0.1) †	3.1(0.1)*
sf36	Mean Score	69.4(1.3)	74.1(1.2)‡,§	73.7(1.2)‡	71.4(1.4)
	Overall Health	65.9(1.7)	71.0(1.4) †	71.7(1.6)‡,§	68.7(1.6)
	Functional Status	77.6(1.8)	81.0(1.5)	80.0(1.7)	77.0(1.9)
	Well-being	65.1(1.4)	71.5(1.3)‡,π	68.8(1.2)*	67.7(1.4)

All data are mean(SEM)

Definition of Abbreviations: FOSQ = Functional Outcomes of Sleepiness Questionnaire; sf36 = 36-item Medical Outcomes Study Questionnnaire; Functional Status = mean score of the domains of physical function, role limitations due to physical problems, role limitations due to emotional problems and social functioning; Well-Being = mean score of the domains of mental health, energy/vitality and bodily pain.

	p<0.05	p<0.01	p<0.001
Compared to baseline	*	†	‡
Compared to placebo	§	π	¶
CPAP vs. MAS	**		

Figure E1

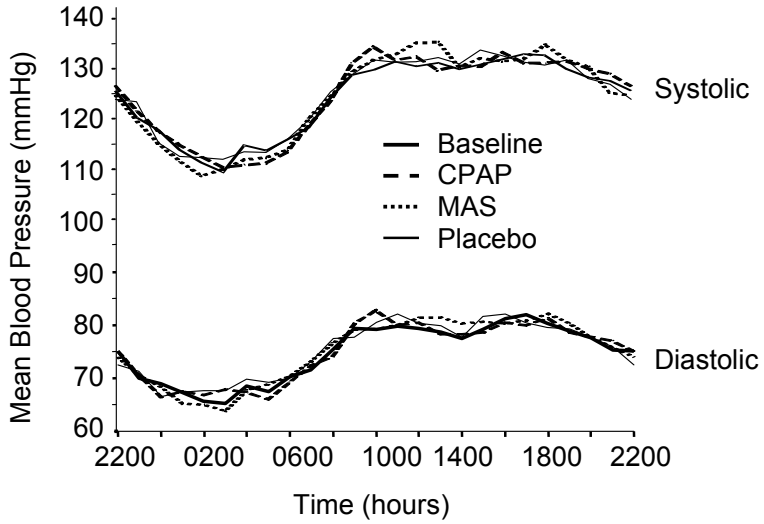
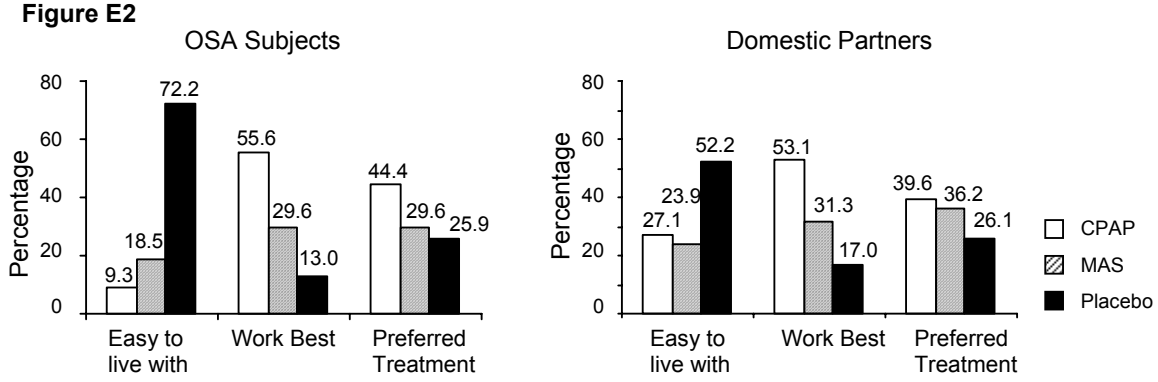

Mean Blood Pressure (mmHg)
140
130
120
110
100
90
80
70
60
2200
0200
0600
1000
1400
1800
2200
Time (hours)
Baseline
CPAP
MAS
Placebo
Systolic
Diastolic

Figure E2


OSA Subjects
Domestic Partners
Percentage
80
60
40
20
0
9.3
18.5
72.2
55.6
29.6
13.0
44.4
29.6
25.9
27.1
23.9
52.2
53.1
31.3
17.0
39.6
36.2
26.1
Easy to live with
Work Best
Preferred Treatment
CPAP
MAS
Placebo